Understanding telomere diseases through analysis of patient-derived iPS cells.

Journal: Curr Opin Genet Dev

Publication Year: 2013

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PubMed link: 23993228

Funding Grants: Self-renewal and senescence in iPS cells derived from patients with a stem cell disease

Public Summary:
A unique characteristic of tissue stem cells is the ability to self-renew, a process that enables the life-long maintenance of many organs. Stem cell self-renewal is dependent in part on the synthesis of telomere repeats by the enzyme telomerase. Defects in telomerase and in genes in the telomere maintenance pathway result in diverse disease states, including dyskeratosis congenita, pulmonary fibrosis, aplastic anemia, liver cirrhosis and cancer. Many of these disease states share a tissue failure phenotype, such as loss of bone marrow cells or failure of pulmonary epithelium, suggesting that stem cell dysfunction is a common pathophysiological mechanism underlying these telomere diseases. Studies of telomere diseases in undifferentiated iPS cells have provided a quantitative relationship between the magnitude of biochemical defects in the telomerase pathway and disease severity in patients, thereby establishing a clear correlation between genotype and phenotype in telomere disease states. Modeling telomere diseases in iPS cells has also revealed diverse underlying disease mechanisms, including reduced telomerase catalytic activity, diminished assembly of the telomerase holoenzyme and impaired trafficking of the enzyme within the nucleus. These studies highlight the need for therapies tailored to the underlying biochemical defect in each class of patients.

Scientific Abstract:
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